Cognition in Childhood Dystonia

Coenen, Maraike A; Eggink, Hendriekje; Tijssen, M.A.; Spikman, Jacoba

Published in:
Developmental Medicine and Child Neurology

DOI:
10.1111/dmcn.13632

Cognition in childhood dystonia: a systematic review

MARAIKE A COENEN | HENDRIEKJE EGGINK | MARINA A TIJSSEN | JACOBA M SPIKMAN

Department of Neurology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands.

Correspondence to Maraike A Coenen at Department of Neuropsychology, University of Groningen, University Medical Center Groningen, Hanzeplein 1, Poortweg 4, 4th floor, Room V4.131, P. O. Box 30.001, 9700 RB Groningen, the Netherlands. E-mail: m.a.coenen@umcg.nl

This article is commented on by Adegboye on page 216 of this issue.

PUBLICATION DATA
Accepted for publication 20th October 2017.
Published online 14th December 2017.

ABBREVIATIONS

DBS	Deep brain stimulation
IEM	Inborn errors of metabolism

AIM Cognitive impairments have been established as part of the non-motor phenomenology of adult dystonia. In childhood dystonia, the extent of cognitive impairments is less clear. This systematic review aims to present an overview of the existing literature to elucidate the cognitive profile of primary and secondary childhood dystonia.
METHOD Studies focusing on cognition in childhood dystonia were searched in MEDLINE and PsychInfo up to October 2017. We included studies on idiopathic and genetic forms of dystonia as well as dystonia secondary to cerebral palsy and inborn errors of metabolism.
RESULTS Thirty-four studies of the initial 527 were included. Studies for primary dystonia showed intact cognition and IQ, but mild working memory and processing speed deficits. Studies on secondary dystonia showed more pronounced cognitive deficits and lower IQ scores with frequent intellectual disability. Data are missing for attention, language, and executive functioning.
INTERPRETATION This systematic review shows possible cognitive impairments in childhood dystonia. The severity of cognitive impairment seems to intensify with increasing neurological abnormalities. However, the available data on cognition in childhood dystonia are very limited and not all domains have been investigated yet. This underlines the need for future research using standardized neuropsychological procedures in this group.

Dystonia is a hyperkinetic movement disorder characterized by involuntary contractions of opposing muscles resulting in deviating movement and/or postures.[1] It can be classified into primary and secondary dystonia. Primary dystonia is defined as no neurological abnormalities visible on brain scans obtained through magnetic resonance imaging (MRI), including inherited and idiopathic forms of childhood dystonia. Secondary dystonia is defined as neurological abnormalities visible on brain MRI, including patients with focal lesions (e.g. patients with dyskinetic cerebral palsy [CP]) and patients with more diffuse lesions (e.g. patients with inborn errors of metabolism [IEM]).

Traditionally, dystonia has been considered a pure motor disorder resulting from basal ganglia dysfunction.[2] However, similar to other basal ganglia syndromes as Parkinson's and Huntington's disease, non-motor features (e.g. cognitive deficits, pain, fatigue, sleep problems, and psychiatric problems) appear to be an integral component of the phenotype of dystonia and may contribute even more to the perceived burden of the disorder than motor symptoms.[3] Specifically, the occurrence of cognitive deficits is supported by the basal ganglia's dense connections to the prefrontal cortex, involved in the regulation of complex cognitive skills and behavior.[4,5] Dysfunctional connections between the basal ganglia and the prefrontal cortex might explain cognitive deficits.[1,6]

With regard to cognition in dystonia, previous studies have demonstrated mild cognitive deficits in adult patients with idiopathic dystonia in the domains of visuospatial functioning, verbal memory, and set shifting.[7] Adult patients with dystonia in combination with other neurological disorders have been investigated, but because of vastly different methods no conclusions can be drawn so far.[7]

Childhood dystonia often differs in its presentation from adult dystonia. For instance, childhood dystonia is prone to becoming generalized and is more often secondary to other neurological disorders. The question arises whether these differences between children and adults with dystonia also entail differences in non-motor symptoms. This might also shed a light over the question whether cognitive problems are part of the childhood dystonia phenotype and, if so, which cognitive problems are associated with the disorder. The answer to this question has potential implications for diagnosis and treatment. If cognitive deficits are part of the dystonia phenotype, patients might benefit from cognitive rehabilitation comparable to other neurological disorders. If these deficits develop as a consequence of the motor disorder, early intervention and treatment of the motor symptoms is important to prevent cognitive deficits later in life.

 DOI: 10.1111/dmcn.13632

We aimed to conduct a systematic review that structures and evaluates existing literature on cognition in childhood dystonia.

With this systematic review we aim to provide an overview of the current state of research on cognitive deficits in children and adolescents with primary and secondary forms of dystonia, especially in the domains of memory, attention and processing speed, executive functioning, social cognition, and language. Herein we follow the advice of Jahanshahi et al. who advised researchers to cover these cognitive domains and also measure intelligence.[7] We also aim to evaluate the strength of the presented evidence by taking into account the sample size, method of assessment of cognitive functioning, and use of a control group.

What this paper adds

- There is limited data on cognition in childhood dystonia.
- Primary dystonia showed intact cognition and IQ, but mild working memory and processing speed deficits.
- Secondary dystonia showed more pronounced deficits and lower IQ, with frequent intellectual disability.
- There is a strong need for case–control studies assessing cognition using standardized neuropsychological tests.

METHOD

Search strategy

We conducted a systematic literature search according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method. The population we were interested in consisted of patients with idiopathic dystonia, genetically defined dystonia (for an overview see Peall et al.),[3] dystonia caused by IEM (for an overview see van Egmond et al.),[8] or CP. We defined the interest as cognition and the context as early onset, that is children and young adults. Our search terms can be found in Table I.

Inclusion criteria

We used PubMed and PsycInfo for our literature search. One of the authors (MAC) reviewed the titles and abstracts of the 527 initial results based on the following criteria that were discussed with all authors beforehand. The article had to be published in English before October 2017 and had to be available online. Studies about the effectiveness of treatment were included if baseline assessment of cognitive functioning was reported. Studies on secondary dystonia went through a two-stage process: these studies were included in the tables if they met our inclusion criteria but we only describe them in the text if they either exclusively concern patients with dystonia due to another neurological disorder or specify the test results for the group of patients with dystonia within their sample.

Extracted information

From the included articles, we extracted the following data: sample size, mean age of the sample, type of dystonia, type of assessment, results of the assessment of cognitive functioning, and use of a control group. The results were grouped according to the method used by Peall et al.[3] into case reports, smaller case series ($n<5$), larger case series ($n\geq5$), and case–control studies. Test scores are described as extremely low, borderline, low average, average, high average, superior, or very superior, according to the proposed classification by Wechsler (Wechsler Adult Intelligence Scale-III).[9] Herein, we consider borderline scores and extremely low scores as an indication of an impairment.

Grouping of results

In the text we will only discuss primary sources that are case–control studies and larger case series as these studies provide

Table I: Search terms used in the literature search

Specify type of dystonia		
	Secondary dystonia	
Primary dystonia	Diffuse lesions	Focal lesions
Dystonia OR idiopathic-dystonia OR DYT1 OR DYT2 OR DYT3 OR x-linked-dystonia-parkinsonism OR DYT4 OR whispering-dysphonia OR DYT5 OR dopa-responsive-dystonia OR segawa-syndrome OR segawa-disease OR DYT6 OR DYT7 OR DYT8 OR paroxysmal-dystonia OR non-kinesigenic-dyskinesia OR DYT10 OR PRRT2 OR episodic-kinesigenic-dyskinesia OR DYT11 OR myoclonus-dystonia OR DYT12 OR rapid-onset-dystonia-parkinsonism OR DYT13 OR DYT15 OR DYT16 OR DYT17 OR DYT18 OR glut1-deficiency-syndrome OR DYT20 OR DYT21 OR DYT23 OR DYT24 OR DYT25 OR hereditary-dystonia OR primary-dystonia	Dystonia* AND Metabolic-diseases OR Organic-aciduria* OR Organic-acidemia* OR Inborn-errors-of-metabolism	Cerebral-palsy AND Dystonia
Specify cognitive deficits		
Cognitive-functioning OR Cognition OR Neuropsychology OR Neurocognition OR Intelligence OR Memory OR Attention OR Information-processing-speed OR Executive-functions OR Social-cognition OR Language OR Non-motor-symptom		
Specify age group (children, adolescents, and young adults)		
Early-Onset OR Young-Onset OR Children OR Adolescent OR Young-adult		

stronger evidence. We will structure the results according to the type of assessment: (1) standardized neuropsychological assessments, (2) intelligence measurement (usually IQ), (3) experimental designs. Within each of these sections, evidence is structured according to two etiological groups, namely patients with primary and secondary dystonia. We are aware of the recent classification system by Albanese et al.[1] However, as most of the existing literature uses the older classification of primary and secondary dystonia, and in order to increase clarity and readability, we decided to also use the old classification.

RESULTS

Our literature search yielded 665 initial results and the subsequent steps are illustrated in Figure 1. After removal of 138 duplicates, the title and abstract of the remaining 527 articles were screened leading to 34 articles that met our inclusion criteria. A schematic summary of our findings can be found in Figure 2.

Standardized neuropsychological assessments

Primary dystonia

Table II shows the included studies that used standardized neuropsychological assessments. An extensive neuropsychological assessment was performed in a retrospective larger case series with 13 children (mean age=11y 6mo, range 6–18; 7 males) with primary dystonia as part of a screening before deep brain stimulation (DBS) treatment.[10] Four of these children had a *DYT1* mutation, three had a dystonia plus syndrome, and the etiology was unknown in six children. No control group was involved in this study. Individual scores varied greatly, but mean scores showed that working memory is on a low average level and processing speed a low average to borderline level, indicating mild impairments in these functions. Verbal comprehension, perceptual organization, and verbal and visual memory were found to be intact. However, the data set contains many missing values and the patients with dystonia plus syndromes especially, could not complete all tasks.

Secondary dystonia

Owen et al. also investigated children with secondary dystonia using a neuropsychological test battery in a retrospective longitudinal study.[11] Their sample consisted of 40 children (mean age=12y 6mo, range 5–18; 19 males) with different forms of secondary dystonia, including dyskinetic CP (n=22) and dystonia caused by IEM (n=12). All patients

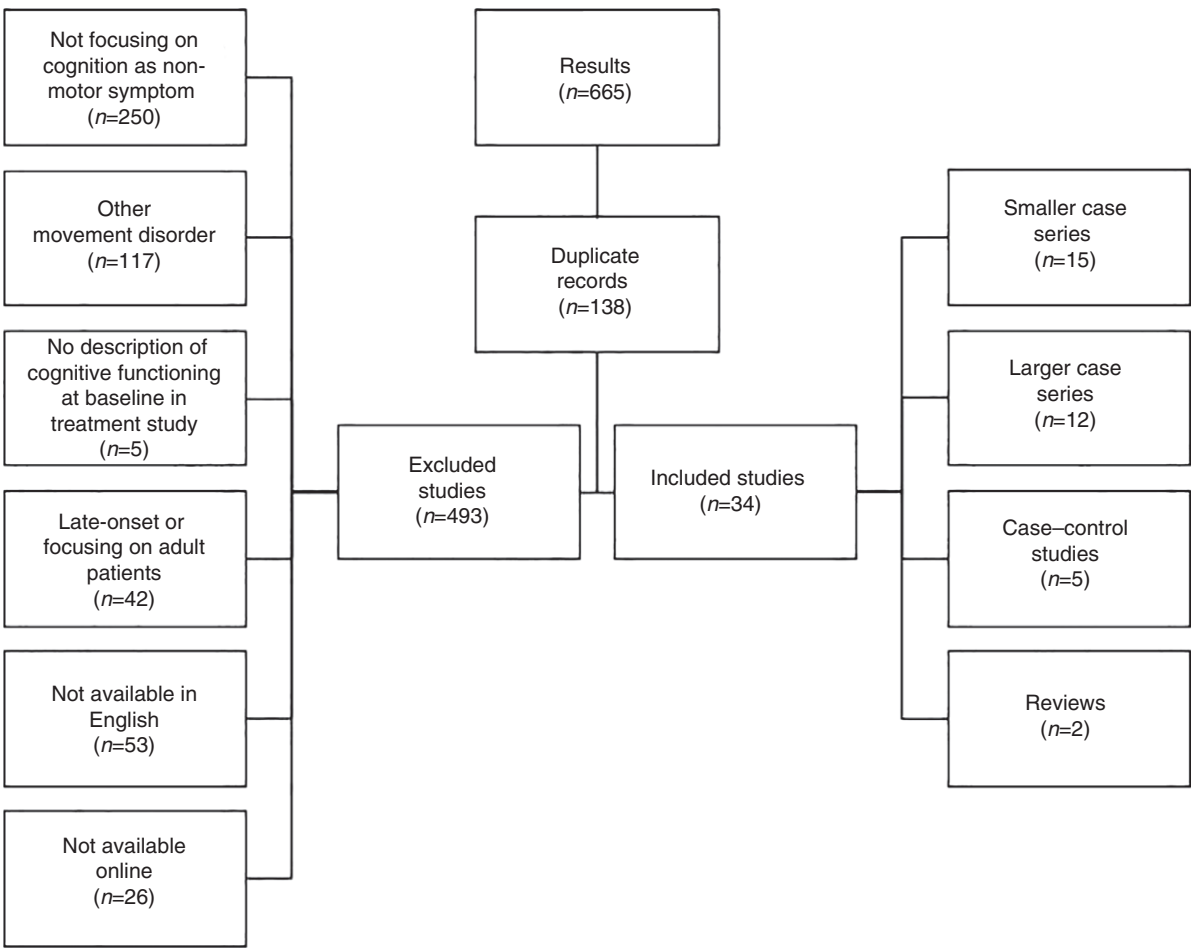

Figure 1: Process of inclusion and exclusion of articles.

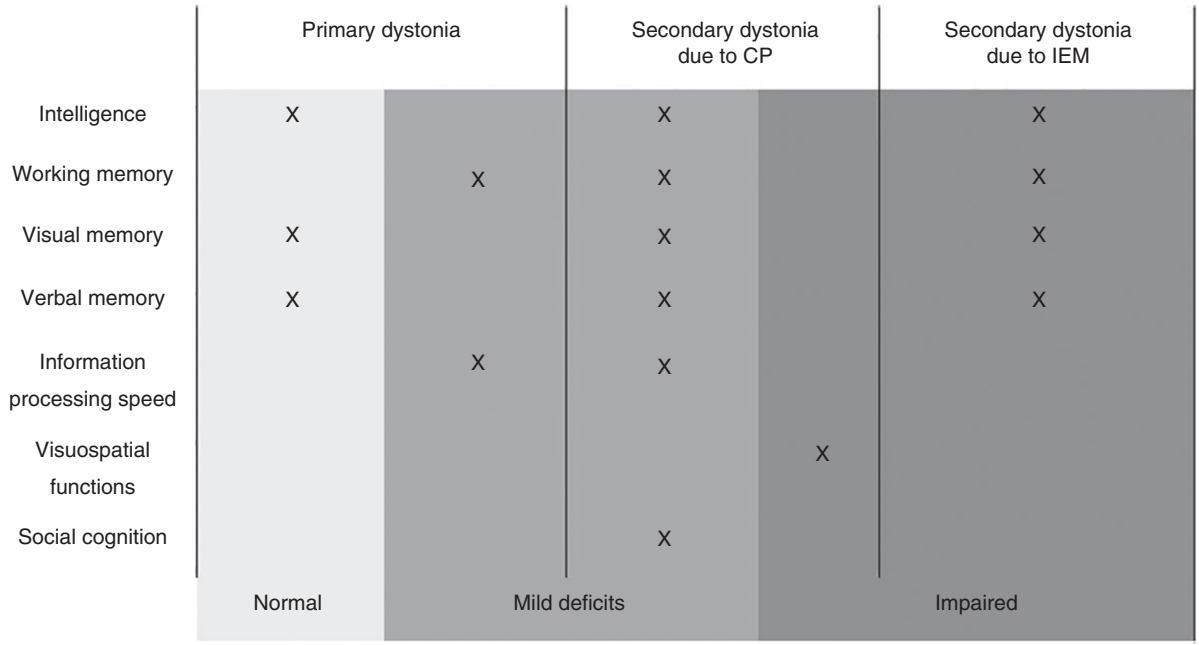

Figure 2: Simplified graphical representation of the results for each group. Missing crosses in a row indicate lack of data. CP, cerebral palsy; IEM, inborn errors of metabolism.

underwent DBS surgery. Verbal comprehension and working memory were found to be average, perceptual reasoning and visual and verbal memory were low average. Falkman et al.[12] investigated theory of mind in a prospective longitudinal case–control study with three patients with dyskinetic CP (mean age=6y 1 mo, range 5–7; 1 male). Their results showed a delayed yet normally patterned development of theory of mind.

One larger prospective longitudinal case series investigated cognitive functioning in children with more diffuse neurological lesions caused by IEM. Seven children with dystonia secondary to pantothenate kinase-associated neurodegeneration (mean age=11y 7mo, range 8–17; 2 males) were included in a study on the effectiveness of DBS by Mahoney et al.[13] Four of these children completed a neuropsychological assessment; severe motor impairment prevented neuropsychological assessment in the other patients. The results showed impairments in verbal and non-verbal reasoning as well as memory. Other cognitive domains were not assessed. These data again concern patients eligible for DBS surgery, which might imply that these patients represent a more severely affected group of patients.

Conclusion

We can conclude that patients with primary dystonia (mainly *DYT1* mutation) show intact verbal comprehension, perceptual organization, and memory while there are mild impairments in working memory and processing speed. Patients with secondary dystonia caused by focal lesions show more serious impairments concerning perceptual reasoning, verbal, and visual memory. No firm conclusions can be drawn about theory of mind as the available data were obtained from a sample of only three children. Most pronounced deficits, problems concerning verbal and non-verbal reasoning as well as memory, are reported in patients with secondary dystonia caused by more diffuse lesions due to pantothenate kinase-associated neurodegeneration.

Intelligence measurement

Primary dystonia

Table III shows the included studies concerning intelligence or school performance. This includes one larger retrospective case series with a sample of 14 primary dystonia children (mean age=9y 8mo, range 6–16; 5 males) from 11 families with torsion dystonia.[14] The authors compared intelligence tests between the patient group, their siblings without clinical symptoms, and an age, sex, and religion-matched healthy control group. The exact tests used were not reported. The authors reported a significantly higher IQ in the patients with dystonia in comparison to healthy controls, where there was no difference in IQ between unaffected siblings and healthy controls.

A retrospective larger case series was conducted on 18 patients with focal hand dystonia caused by a duplication of the *aristaless-related homeobox* gene. Demographic characteristics are available for only 10 of the 18 patients (mean age=16y 6mo, range 5–35; 18 males).[15] Unfortunately, the methods of this study are reported incoherently, so conclusions are difficult to draw.

Table II: Included studies that have used standardized neuropsychological assessments

Author (y)	Patient group (*n*)	Mean age y:mo (range)	Sex	Study design	Cognitive function	Instruments	Results of assessment
				Primary dystonia			
Owen et al. (2015)[10]	Primary dystonia (13)	11:6 (6–18)	7 males, 6 females	Retrospective larger case series on the effect of DBS	Verbal comprehension	WISC-IV	Borderline to high average
					Perceptual organization	WISC-IV	Borderline to high average
					Working memory	WISC-IV	Low average
					Processing speed	WISC-IV	Borderline to low average
					Visual memory	CMS & WMS	Average to high average
					Verbal memory	CMS & WMS	Low average to high average
				Secondary dystonia			
Owen et al. (2017)[11]	Dyskinetic CP, dystonia caused by IEM (40)	12:6 (5–18)	19 males, 21 females	Retrospective longitudinal study on effect of DBS	Verbal comprehension and working memory	WISC-IV & WASI	Average
					Perceptual reasoning and memory	WISC-IV & WASI CMS & WMS	Low average
Falkman et al. (2005)[12]	CP (6; 3 dyskinetic CP)	6:1 (5–7)[a]	1 male, 2 females[a]	Prospective longitudinal case–control study	ToM	Pretend play Perception Part-whole Desire First & Second order false belief tasks	Delayed yet normal patterned development of ToM, especially first order false belief tasks ($p<0.008$) in children with dyskinetic CP compared to a healthy control group
Adegboye et al. (2017)[28]	CP (22; 19 dyskinetic CP)	13:0 (8–17)	12 males, 10 females	Cross-sectional study	Test for ToM, emotion, behavior and social difficulties, Non-verbal reasoning, perceptual reasoning	RMET Emotion regulation Checklist, SDQ RSPM WISC-IV	More problems concerning ToM ($p<0.001$) and social development ($p=0.018$) in patients than in healthy controls Results for dyskinetic CP patients not specified
Dahlgren Sandberg (2006)[19]	CP (6; 3 dyskinetic CP)	6:5 (5–7)	1 male, 5 females	Prospective longitudinal study	Working memory tests	Digit Span Corsi Blocks	Decreased working memory abilities in comparison with the control group, *p*-value not reported
Gagliardi et al. (2011)[18]	CP (64; 2 dyskinetic CP)	8:10 (4–14)	38 males, 26 females	Observational case–control study	Visuoperceputal skills Visuospatial skills Sequence learning	Corsi blocks WPPSI, WISC-R, & WAIS-R	Patients distribute over two groups: high functioning group with intact sequencing learning and low functioning group with impaired sequencing learning, lower IQ and worse visuoperceptual and visuospatial skills
Mahoney et al. (2011)[13]	Dystonia secondary to PKAN (7)	11:7 (8–17)	2 males, 5 females	Prospective longitudinal case series	Verbal reasoning and non-verbal reasoning & memory	WISC-IV, WISC-III, WASI, & WPPSI, BPVS-II, CMS, & Nepsy –II	Results for four patients: Borderline to low average
Isaac et al. (2008)[32]	PKAN (1)	16:0	Male	Case report	Visual perception, receptive language skills, non-verbal reasoning	Visual Object and Space perception Test, BPVS, & Matrix reasoning WASI	Visual perception average non-verbal reasoning borderline delay in development of receptive language

[a]Age and sex calculated for patients with dystonia only. DBS, deep brain stimulation; WISC-R/-III/-IV, Wechsler Intelligence Scale for Children – Revised/-Third edition/-Fourth edition; CMS, Children's Memory Scale; WMS, Wechsler Memory Scale; CP, cerebral palsy; IEM, inborn errors of metabolism; WASI, Wechsler Abbreviated Scale of Intelligence; ToM, theory of mind; RMET, Reading the Mind in the Eyes Test; SDQ, Strength and Difficulties Questionnaire; RSPM, Raven's Standard Progressive Matrices; WPPSI, Wechsler Preschool and Primary Scale of Intelligence; WAIS-R, Wechsler Adult Intelligence Scale – revised; PKAN, pantothenate kinase-associated neurodegeneration; BPVS-II, British Picture Vocabulary Scale – Second edition; Nepsy-II, A Developmental Neuropsychological Assessment – Second edition.

Table III: Included studies concerning intelligence measurement

Author (year)	Patient group (*n*)	Mean age y:mo (range)	Sex	Study design	Type of assessment	Results of assessment
			Primary dystonia			
Eldridge et al. (1970)[14]	Torsion dystonia (101; 14 with psychological assessment)	9:8 (6–16)	5 males, 9 females	Retrospective case series	Intelligence based on patient history	Higher IQ in the patient group compared to healthy controls (p<0.030)
Szczaluba et al. (2006)[15]	Focal hand dystonia in patients with *ARX* gene duplication (18; 10 with demographic data)	16:6 (5–35)	18 males	Retrospective larger case series	WISC-IV & WAIS-III, Terman-Merrill scales	Borderline
Dale et al. (2011)[33]	Myoclonus dystonia (6; one family, one child)	17:0[a]	Female[a]	Case reports	WISC-III	Borderline
Szymańska et al. (2014)[34]	Different forms of IEM and neurodevelopmental disorders (7; 2 patients with dystonia: DYT-1 and idiopathic)	23:0 (21–26)[a]	1 male, 1 female[a]	Case reports	Intelligence based on patient history	Average
Labate et al. (2012)[35]	Paroxysmal kinesigenic dystonia (2)	11:6 (7–16)[a]	2 males[a]	Case reports	WISC (unclear which version)	Intellectual disability in both cases
Crosiers et al. (2011)[36]	Juvenile dystonia-parkinsonism (1)	12:0	Male	Case report	WISC-III	Intellectual disability
			Secondary dystonia			
Broggi et al. (1983)[16]	CP (33; 11 with dyskinetic CP)	15:10 (12–21)[a]	6 males, 5 females[a]	Prospective longitudinal case series on effect of thalamotomy	WISC (unclear which version) or if motor impairment was too severe Raven test Neuropsychological tests covering memory, visual perception and language Rorschach test	Results for patients with dyskinetic CP: Borderline to high average
Ben-Pazi (2011)[17]	Dyskinetic CP (35)	8:10 (6mo–19y)	21 males, 14 females	Retrospective larger case series on effect of anticholinergic medication	Intelligence estimated based on school type	34/35 patients assumed borderline
Gagliardi et al. (2011)[18]	CP (64; 2 with dyskinetic CP)	8:10 (4–14)	38 males, 26 females	Observational case–control study	WPPSI, WISC, WAIS	Lower IQ in patients than controls (p<0.010) Patients distribute over two groups: high functioning group with intact sequencing learning and low functioning group with impaired sequencing learning, lower IQ and worse visuoperceptual and visuospatial skills

Table III: Continued

Author (year)	Patient group (*n*)	Mean age y:mo (range)	Sex	Study design	Type of assessment	Results of assessment
Dahlgren Sandberg (2006)[19]	CP (6; 3 with dyskinetic CP)	6:5 (5–7)	1 male, 5 females	Prospective longitudinal study	Experimental task: Linguistic capabilities Working memory tests	Decreased reading, spelling and working memory abilities in comparison with the control group (no *p*-values reported), yet development over they
Falkman et al. (2005)[12]	CP (6; 3 dyskinetic CP)	6:1 (5–7)[a]	1 male, 2 females[a]	Prospective longitudinal case–control study	Raven's Progressive Matrices Coloured version	IQ used as matching criterion (borderline to average), no difference with control group (p=0.656)
Bodensteiner & Johnsen (2004)[37]	CP (10; 4 with dyskinetic CP)	Unknown (7 m–18y)	Unknown	Retrospective observational study	Intelligence based on patient history	9/10 patients assumed borderline
Bottos et al. (2001)[38]	CP (29; 3 with dyskinetic CP)	6:2 (3–8)	12 males, 17 females	Intervention study on the effect of powered wheelchairs	Leitner International Performance Scale and Peabody Developmental Verbal Scale	Mean IQ borderline before treatment
Marlow (2004)[39]	CP (review)	Unknown	Unknown	Review	Review	Development borderline
Vogels et al. (1994)[40]	Left-sided thalamic lesion (1)	9:0	Female	Case report	IQ measurement	IQ average, receptive language skills average, expressive language borderline
López-Laso et al. (2011)[20]	Dopa-responsive dystonia (14; two families, 7 children)	10:7 (4–16)[a]	4 males, 6 females[a]	Larger prospective observational case series	WISC-R, WAIS-III, WPPSI	Borderline to high average
Neville et al. (2005)[21]	Dopa-responsive dystonia (7)	7:5 (11 m-14y)	4 males, 3 females	Observational case study	Unknown	Borderline
Ebrahimi-Fakhari et al. (2015)[41]	Dopa-responsive dystonia (1)	15:0	Male	Case report	IQ measurement	Low average
Kyllerman et al. (1994)[42]	Glutaric aciduria type I (12; 10 with dystonia)	11:9 (5–16)[a]	4 males, 6 females	Case reports	Coloured Progressive Matrices, Peabody Picture Vocabulary Test	8 patients underwent neuropsychological testing. IQ: borderline to average
Nicolaides et al. (1998)[22]	Methylmalonic aciduria (35; 5 with dystonia all of whom did not respond to cobalamin)	Unknown	Unknown	Cross-sectional study	WISC-III, British Ability Scales, Bayley Scales of Infant Development, Ruth Griffiths Developmental Scales	cobalamin responders IQ: average Cobalamin non-responders and onset in 1st month of life: IQ low average
Shevell et al. (1993)[43]	Methylmalonic aciduria (20; 1 with dystonia; data on psychological assessment only for other patients)	9:0[a]	Unknown	Observational study	Intelligence based on patient history	No results available for dystonia patient
Jinnah et al. (2010)[23]	Lesch-Nyhan disease (46; 21 with dystonia)	21:2 (3–45)[a]	21 males[a]	Prospective larger case series	IQ unclear method	IQ scores for 13 patients with dystonia low average
Mengel et al. (2013)[44]	Nieman-Pick Type C (review)	Unknown	Unknown	Review	Review	In children delay of cognitive development and later cognitive decline

Table III: Continued

Author (year)	Patient group (*n*)	Mean age y:mo (range)	Sex	Study design	Type of assessment	Results of assessment
Ito et al. (2011)[24]	Glut-1 deficiency (6; 5 with dystonia)	15:1 (10–19)[a]	5 males[a]	Prospective larger case series on effect of modified Atkins diet	Tanaka-Binet Scale, Tsumori-Inage Scale, WISC-III	IQ scores for 4 patients with dystonia: borderline
Gumus et al. (2015)[25]	Glut-1 deficiency (6; 2 with dystonia)	7:0 (2–11)[a]	2 males[a]	Prospective larger case series	WISC-IV, Stanford-Binet Intelligence Scale for Children younger than 6 years of age	IQ score for one patient with dystonia: borderline
Klepper et al. (2003)[45]	PKAN (1)	12:0	Male	Case report	School performance	Difficulties in emotional control and academic skills, cognitive decline

[a]Age and sex calculated for patients with dystonia only. ARX, aristaless-related homeobox; WISC-R/-III/-IV, Wechsler Intelligence Scale for Children – Revised/-Third edition/-Fourth edition; WAIS, Wechsler Adult Intelligence Scale; IEM, inborn errors of metabolism; WASI, Wechsler Abbreviated Scale of Intelligence; CP, cerebral palsy; WPPSI, Wechsler Preschool and Primary Scale of Intelligence; PKAN, pantothenate kinase-associated neurodegeneration.

Secondary dystonia

Only one larger prospective longitudinal case series that investigated intelligence in children with CP reported the test results for patients with dyskinetic CP specifically (*n*=11, mean age=15y 10mo, range 12–21; 6 males).[16] The patients in this sample underwent stereotaxic thalamotomy and presurgery results show a high prevalence of intellectual disability in this group and mean IQ scores in the low average area. These results are in line with another large retrospective case series[17] on the effectiveness of anticholinergic medication on dystonia in children with CP. At baseline, cognition was estimated based on school type and results showed probable intellectual disability in 33 out of 35 patients (mean age=8y 10mo, range 6mo–19y; 21 males).

Only three of the presented studies in this section included a control group.[12,18,19] However, two do not specify which results apply to the subgroup of patients with dyskinetic CP within their sample.[18,19] The third study concerns a prospective longitudinal case–control study with three patients with dyskinetic CP (mean age=6y 1mo, range 5–7; 1 male).[12] Their IQ scores ranged from intellectual disability to average.

Eleven studies looked into intelligence of children with dystonia based on IEM. Intelligence of patients with dopa-responsive dystonia was investigated in one larger prospective case series (14 patients, 7 children: mean age=10y 7mo, range 4–16; 4 males)[20] and an observational study describing seven children with dopa-responsive dystonia (mean age=7y 5mo, range 11mo–14y; 4 males).[21] Intelligence was found to be in the range of intellectual disability and low average. In patients with methylmalonic aciduria, two groups can be distinguished based on whether or not they respond positively to treatment with cobalamin. In this cross-sectional study, none of the patients with dystonia (*n*=5, age and sex not reported) responded to cobalamin and showed a borderline IQ. No control group was included.[22] One prospective larger case series on patients with Lesch-Nyhan disease showed IQ scores ranging from mild impairment to low average in 11 patients with dystonia. No data were available for nine other dystonic patients (mean age=21y 2mo, range 3–45; 20 males).[23] For patients with dystonia secondary to Glut-1 deficiency, verbal and performance IQ have been shown to be in the range of intellectual disability.[24,25] This was shown in a prospective larger case series on effects of modified Atkins diet 5 with dystonia (mean age=15y 1mo, range 10–19; 5 males)[24] and a prospective larger case series with six patients, but only two with dystonia (mean age=7y, range 2–11; 2 males).[25] Unfortunately, this last study reported IQ scores for only one patient.

Conclusion

In summary, the presented literature points to intact IQ in patients with torsion dystonia and lower IQ, with frequent intellectual disability, in patients with secondary dystonia. However, most studies have small sample sizes which prevent generalizations of these findings.

Table IV: Included studies using experimental designs

Author (year)	Patient group (*n*)	Mean age y:mo (range)	Sex	Study design	Cognitive domain	Results of assessment
			Primary dystonia			
Mayor-Dubois et al. (2010)[26]	Basal ganglia pathology (18; 2 with idiopathic dystonia)	8:0 (7–9)[a]	1 male, 1 female[a]	Experiment	Memory	Patients with idiopathic dystonia: procedural learning difficulties
			Secondary dystonia			
Boy et al. (2015)[27]	Glutaric aciduria type I (30; 13 with dystonia)	Unknown (5–29)	18 males, 12 females	Prospective case–control study	Attention and working memory	Preserved information processing if no demand on motor speed

[a]Age and sex calculated for patients with dystonia only.

Experimental tasks

Primary dystonia

Table IV shows the studies using experimental tasks that were included in this systematic review. Mayor-Dubois et al.[26] conducted an experiment on procedural learning in children with basal ganglia pathology. They used a task focusing on visuomotor sequence learning and classification skills in 18 children (mean age=11y 6mo, range 8–15; 9 males) with varying basal ganglia pathology and normal cognitive functioning (i.e. an IQ in the average range). Two patients had idiopathic progressive dystonia (mean age=8y, range 7–9; 1 male), and showed more problems with the motor aspects (procedural learning) than with the cognitive aspects (classification) of the task. The authors speculate that their results suggest a highly specific dysfunction of motor pathways in the cortex-basal ganglia-cortex circuits as opposed to other disorders with basal ganglia involvement.

Secondary dystonia

Boy et al.[27] investigated information processing of 30 children and young adults with glutaric aciduria type I (mean age=unknown, range 5–29y; 18 males) in comparison to a healthy control group (*n*=196, age range 5–28y, 103 males) in a prospective case–control study. In the patient group, 13 children were diagnosed with dystonia secondary to glutaric aciduria type I but the paper does not specify the results for this subgroup, therefore no conclusion can be drawn here.

Conclusion

Concerning patients with primary dystonia, existing literature points towards procedural learning difficulties and intact information processing speed.

DISCUSSION

This systematic review aimed to provide an overview of the current knowledge about cognition in childhood dystonia. We showed that the available data on cognitive functioning in patients with childhood dystonia are very limited. In particular, studies on specific cognitive functions are scarce as the majority of the studies solely focus on IQ. For primary dystonia, we can at the most say that intelligence and most cognitive functions are intact except for mild deficits in working memory and verbal memory. Only one study used standardized neuropsychological tests in this patient group.[10]

In patients with secondary dystonia, mild cognitive deficits as well as cognitive impairments and frequent intellectual disability have been found (see Fig. 2). Mild deficits in memory, information processing speed, and social cognition have been shown in patients with CP. Visuospatial functions were found to be impaired in this group. Patients with secondary dystonia based on IEM were found to have impaired memory functions. However, these results have to be interpreted with caution, as only parts of the described samples consisted of patients with dystonia. Furthermore, not all domains of cognitive functioning have been investigated yet. In three out of four cases, data on neuropsychological functioning were obtained from children who underwent DBS surgery, which implies that their dystonia is not treatable with medication. It is possible that this creates a bias in the samples, in the sense that these patients represent the more severely affected patients with dystonia. It is unclear whether more severe motor impairments are associated with more severe cognitive problems in patients with dystonia.

Memory has been investigated and results show mild working memory deficits in patients with primary dystonia. In patients with secondary dystonia, memory deficits are more pronounced and occur in visual- and verbal- as well as working memory. Here, patients with diffuse neurological lesions show the most pronounced memory deficits compared to patients with primary dystonia and dystonia secondary to CP. Overall, the results on memory match the results found in adult patients.[7] Other domains of cognitive functioning have been investigated less consequently. Visuospatial functions have been assessed in patients with dyskinetic CP only and the results point to an impairment of these functions. Slow information processing has been found in patients with primary dystonia and dystonia caused by CP.

Social cognition was investigated in two studies with children with CP. One study has shown that social cognition is not intact in this patient group.[28] This sample also contained children with dyskinetic CP but as the results were not specified for this subgroup, no conclusion can be drawn considering social cognition in children with dystonia. Still, the results are in line with the results of the other study, a case–control study[12] on social cognition of children with CP. This study suggests a delayed yet normally patterned development of social cognition in children with dyskinetic CP. This conclusion is based on three children and therefore cannot be generalized. No results for the domains of attention, language, and executive functioning have been reported in the literature for any of the patient groups described here, leaving a gap in our knowledge of the cognitive functioning of these patients.

We have discussed intelligence measurements separately, because the resulting IQ may only partially reflect functioning in daily life.[29] Intelligence is a psychological construct that is difficult to define. Generally, the discussion revolves around the question of whether intelligence should be considered one single concept (g-factor) or several related factors. Today, most intelligence tests are a representation of the former idea (g-factor).[30] Commonly used intelligence tests for children are not developed to measure specific cognitive domains and several aspects of cognitive functioning are missing from these tests, for example executive functioning and social cognition. The manuals of intelligence tests require a strongly structured testing environment which is necessary to achieve reliable results but at the same time does not match situations in daily life.

Concerning intelligence, the limited results (14 children) in primary childhood dystonia show a higher IQ compared to healthy controls. Unfortunately, the intelligence test used is not reported, which prevents an evaluation of the reliability of the results. In addition, this finding has not been replicated since 1970 and the findings cannot be generalized as the sample size was small. Intelligence is mostly average in patients with primary dystonia, but patients with secondary dystonia caused by CP often have an IQ below average. In patients with secondary dystonia caused by IEM, intellectual disability frequently occurs.

Of the studies included, 17 were larger case series or case–control studies presenting relatively stronger evidence than single case studies. However, the assessment tools differ greatly between the studies and not all studies assess the same domains of cognitive functioning. Furthermore, not all cognitive domains have been investigated yet. Data are missing on attention, language, and executive functioning. The domain of social cognition has not yet been sufficiently investigated in young patients with dystonia.

As we have stated above, knowing more about the cognitive profile of young patients with dystonia enables clinicians to adapt their treatment strategies to the individual patients. Additionally, identifying cognitive problems is important for the detection of possible impairments and initiation of support in order to enable a positive course of development. With this systematic review, we have sought to describe the cognitive profile of childhood dystonia. More research is needed to complete this profile and enable clinicians to make full use of it for clinical practice.

The scarcity of the available data can reflect three things: (1) the low prevalence of dystonia, which makes it difficult to find homogeneous patient groups big enough to draw sound conclusions; (2) the difficulties of diagnosing dystonia which becomes particularly evident in the studies with patients with secondary dystonia where it is not always clear how many patients were also diagnosed with dystonia; (3) the difficulties that arise when conducting a neuropsychological assessment with patients with severe motor impairments. Neuropsychological tests are not designed to be used in this patient group and necessary adjustments in the testing procedure can invalidate the results. This makes the use of a control group obligatory. In this systematic review, we have identified only five case–control studies in the 34 included studies. This small number of case–control studies underlines the need for further research using standardized neuropsychological testing and control groups. In the five presented case–control studies, test results of patients were compared to results of a healthy control group. Following Macerollo et al.,[31] it is possible that there are cognitive deficits inherent to movement disorders in general. Therefore, additional control groups consisting of patients with other movement disorders would help to further elucidate the neuropsychological profile of patients with childhood dystonia.

In addition to the limitations at study level, the current systematic review also has limitations. The naming of dystonia and cognitive problems differs vastly between studies. We have tried to include the most commonly used terms in our key words, but we cannot rule out the possibility that we have missed studies that have used different key words.

CONCLUSION

In summary, there is a strong need for studies assessing cognitive functioning in patients with varying forms of childhood dystonia using standardized neuropsychological methods. So far we know that memory functions are impaired especially in patients with secondary dystonia and that these patients also show lower IQ scores. Other domains of cognitive functioning have been investigated insufficiently. Research should focus on the following domains: memory, attention and processing speed, language, executive functioning, visuospatial skills, and social cognition. Measures or estimations of intelligence are useful to match the patient group to a control group. Future studies need to assess cognitive functioning in young patients more consequently in order to find out if the deficits seen in adults[7] are also present in young patients, how they develop during brain maturation, and which factors

are associated with these deficits. Knowing more about these deficits will help us to tailor treatment plans to the specific needs of individual patients.

ACKNOWLEDGEMENTS

One of the authors (MAC) received research grants from the Phelps Stichting voor spastici, the Stichting Vrienden Beatrix Kinderziekehnhuis, and the Stichting wetenschapsfonds Dystonie. The first grant was shared with the second author (HE). These grants were used for a larger research project on non-motor symptoms in early onset dystonia, part of which is the current systematic review. The named organizations were not involved in the design of this systematic review, the reviewing process itself, or the manuscript preparation. The authors have stated that they had no interests that may be perceived as posing a conflict or a bias.

REFERENCES

1. Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. *Mov Disord* 2013; **28**: 863–73.
2. Zoons E, Booij J, Nederveen AJ, Dijk JM, Tijssen MA. Structural, functional and molecular imaging of the brain in primary focal dystonia – a review. *Neuroimage* 2011; **56**: 1011–20.
3. Peall KJ, Kuiper A, de Koning TJ, Tijssen MA. Non-motor symptoms in genetically defined dystonia: homogenous groups require systematic assessment. *Parkinsonism Relat Disord* 2015; **21**: 1031–40.
4. Geyer HL, Bressman SB. The diagnosis of dystonia. *Lancet Neurol* 2006; **5**: 780–90.
5. Lange F, Seer C, Dengler R, Dressler D, Kopp B. Cognitive flexibility in primary dystonia. *J Int Neuropsychol Soc* 2016; **22**: 662–70.
6. Lumsden DE, Kaminska M, Gimeno H, et al. Proportion of life lived with dystonia inversely correlates with response to pallidal deep brain stimulation in both primary and secondary childhood dystonia. *Dev Med Child Neurol* 2013; **55**: 567–74.
7. Jahanshahi M, Czernecki V, Zurowski AM. Neuropsychological, neuropsychiatric, and quality of life issues in DBS for dystonia. *Mov Disord* 2011; **26**: S63–78.
8. van Egmond ME, Kuiper A, Eggink H, et al. Dystonia in children and adolescents: a systematic review and a new diagnostic algorithm. *J Neurol Neurosurg Psychiatry* 2015; **86**: 774–81.
9. Wechsler D. Wechsler Adult Intelligence Scale-III. San Antonio, TX: The Psychological Corporation, 1997.
10. Owen T, Gimeno H, Selway R, Lin JP. Cognitive function in children with primary dystonia before and after deep brain stimulation. *Eur J Paediatr Neurol* 2015; **19**: 48–55.
11. Owen T, Adegboye D, Gimeno H, Selway R, Lin JP. Stable cognitive functioning with improved perceptual reasoning in children with dyskinetic cerebral palsy and other secondary dystonias after deep brain stimulation. *Eur J Paediatr Neurol* 2017; **21**: 193–201.
12. Falkman KW, Sandberg AD, Hjelmquist E. Theory of mind in children with severe speech and physical impairment (SSPI): a longitudinal study. *Int J Disabil Dev Educ* 2005; **52**: 139–57.
13. Mahoney R, Selway R, Lin JP. Cognitive functioning in children with pantothenate-kinase-associated neurodegeneration undergoing deep brain stimulation. *Dev Med Child Neurol* 2011; **53**: 275–9.
14. Eldridge R, Harlan A, Cooper IS, Riklan M. Superior intelligence in recessively inherited torsion dystonia. *Lancet* 1970; **1**: 65–7.
15. Szczaluba K, Nawara M, Poirier K, et al. Genotype-phenotype associations for ARX gene duplication in X-linked mental retardation. *Neurology* 2006; **67**: 2073–5.
16. Broggi G, Angelini L, Bono R, Giorgi C, Nardocci N, Franzini A. Long term results of stereotactic thalamotomy for cerebral palsy. *Neurosurgery* 1983; **12**: 195–202.
17. Ben-Pazi H. Trihexyphenidyl improves motor function in children with dystonic cerebral palsy: a retrospective analysis. *J Child Neurol* 2011; **26**: 810–6.
18. Gagliardi C, Tavano A, Turconi AC, Pozzoli U, Borgatti R. Sequence learning in cerebral palsy. *Pediatr Neurol* 2011; **44**: 207–13.
19. Dahlgren Sandberg A. Reading and spelling abilities in children with severe speech impairments and cerebral palsy at 6, 9, and 12 years of age in relation to cognitive development: a longitudinal study. *Dev Med Child Neurol* 2006; **48**: 629–34.
20. López-Laso E, Sánchez-Raya A, Moriana JA, et al. Neuropsychiatric symptoms and intelligence quotient in autosomal dominant Segawa disease. *J Neurol* 2011; **258**: 2155–62.
21. Neville BG, Parascandalo R, Farrugia R, Felice A. Sepiapterin reductase deficiency: a congenital dopa-responsive motor and cognitive disorder. *Brain* 2005; **128**: 2291–6.
22. Nicolaides P, Leonard J, Surtees R. Neurological outcome of methylmalonic acidaemia. *Arch Dis Child* 1998; **78**: 508–12.
23. Jinnah HA, Ceballos-Picot I, Torres RJ, et al. Attenuated variants of Lesch-Nyhan disease. *Brain* 2010; **133**: 671–89.
24. Ito Y, Oguni H, Ito S, Oguni M, Osawa M. A modified Atkins diet is promising as a treatment for glucose transporter type 1 deficiency syndrome. *Dev Med Child Neurol* 2011; **53**: 658–63.
25. Gumus H, Bayram AK, Kardas F, et al. The effects of ketogenic diet on seizures, cognitive functions, and other neurological disorders in classical phenotype of glucose transporter 1 deficiency syndrome. *Neuropediatrics* 2015; **46**: 313–20.
26. Mayor-Dubois C, Maeder P, Zesiger P, Roulet-Perez E. Visuo-motor and cognitive procedural learning in children with basal ganglia pathology. *Neuropsychologia* 2010; **48**: 2009–17.
27. Boy N, Heringer J, Haege G, et al. A cross-sectional controlled developmental study of neuropsychological functions in patients with glutaric aciduria type I. *Orphanet J Rare Dis* 2015; **10**: 163–6.
28. Adegboye D, Sterr A, Lin JP, Owen TJ. Theory of mind, emotional and social functioning, and motor severity in children and adolescents with dystonic cerebral palsy. *Eur J Paediatr Neurol* 2017; **21**: 549–56.
29. Bouma A, Mulder J, Kessels R. Wechsler Adult Intelligence Scale – WAIS-III en WAIS-IV. In: Bouma A, Mulder J, Lindeboom J, Schmand B, editors. Handboek Neuropsychologische Diagnostiek. Amsterdam: Pearson Assessment and Information B.V., 2012: 33–76.
30. Eling P, Oosterman J. Intelligentie. In: Kessels R, Eling P, Ponds R, Spikman J, van Zandvoort M, editors. Klinische Neuropsychologie. Amsterdam: Uitgeverij Boom, 2012: 313–31.
31. Macerollo A, Bose S, Ricciardi L, Edwards MJ, Kilner JM. Linking differences in action perception with differences in action execution. *Soc Cogn Affect Neurosci* 2015; **10**: 1121–7.
32. Isaac C, Wright I, Bhattacharyya D, Baxter P, Rowe J. Pallidal stimulation for pantothenate kinase-associated neurodegeneration dystonia. *Arch Dis Child* 2008; **93**: 239–40.
33. Dale RC, Nasti JJ, Peters GB. Familial 7q21.3 microdeletion involving epsilon-sarcoglycan causing myoclonus dystonia, cognitive impairment, and psychosis. *Mov Disord* 2011; **26**: 1774–5.
34. Szymańska K, Szczałuba K, Lugowska A, et al. The analysis of genetic aberrations in children with inherited neurometabolic and neurodevelopmental disorders. *Biomed Res Int* 2014; **2014**: 424796.
35. Labate A, Tarantino P, Viri M, et al. Homozygous c.649dupC mutation in *PRRT2* worsens the BFIS/PKD phenotype with mental retardation, episodic ataxia, and absences. *Epilepsia* 2012; **53**: e196–9.
36. Crosiers D, Ceulemans B, Meeus B, et al. Juvenile dystonia-parkinsonism and dementia caused by a novel ATP13A2 frameshift mutation. *Parkinsonism Relat Disord* 2011; **17**: e135–8.
37. Bodensteiner JB, Johnsen SD. Cerebellar injury in the extremely premature infant: newly recognized but relatively common outcome. *J Child Neurol* 2005; **20**: 139–42.
38. Bottos M, Bolcati C, Sciuto L, Ruggeri C, Feliciangeli A. Powered wheelchairs and independence in young children with tetraplegia. *Dev Med Child Neurol* 2001; **43**: 769–77.
39. Marlow N. Neurocognitive outcome after very preterm birth. *Arch Dis Child Fetal Neonatal Ed* 2004; **89**: F224–8.

40. Vogels OJ, Maassen B, Rotteveel JJ, Merx JL. Focal dystonia and speech impairment responding to anticholinergic therapy. *Pediatr Neurol* 1994; **11**: 346–8.
41. Ebrahimi-Fakhari D, Maas B, Haneke C, et al. Disruption of SOX6 is associated with a rapid-onset dopa-responsive movement disorder, delayed development, and dysmorphic features. *Pediatr Neurol* 2015; **52**: 115–8.
42. Kyllerman M, Skjeldal OH, Lundberg M, et al. Dystonia and dyskinesia in glutaric aciduria type I: clinical heterogeneity and therapeutic considerations. *Mov Disord* 1994; **9**: 22–30.
43. Shevell MI, Matiaszuk N, Ledley FD, Rosenblatt DS. Varying neurological phenotypes among muto and mut- patients with methylmalonylCoA mutase deficiency. *Am J Med Genet* 1993; **45**: 619–24.
44. Mengel E, Klünemann HH, Lourenço CM, et al. Niemann-Pick disease type C symptomatology: an expert-based clinical description. *Orphanet J Rare Dis* 2013; **8**: 166.
45. Klepper J, Schaper J, Raca G, et al. Progressive dystonia in a 12-year-old boy. *Eur J Paediatr Neurol* 2003; **7**: 85–8.